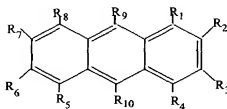


We claim:

1. A method for making a hypermutable cell comprising exposing a cell to an inhibitor of mismatch repair, wherein said inhibitor is an anthracene, an ATPase inhibitor, a nuclease inhibitor, a polymerase inhibitor, or an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.
2. The method of claim 1 wherein said inhibitor is an anthracene.
3. The method of claim 2 wherein said anthracene has the formula:



wherein R<sub>1</sub>-R<sub>10</sub> are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxy carbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO<sub>2</sub>, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and

wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl,

substituted aryl, and substituted heteroaryl are halogen, CN, NO<sub>2</sub>, lower alkyl, aryl, heteroaryl, aralkyl, aralkyloxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino;

and wherein said amino groups optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

4. The method of claim 3 wherein  $R_5$  and  $R_6$  are hydrogen.
5. The method of claim 3 wherein  $R_1$ - $R_{10}$  are independently hydrogen, hydroxyl, alkyl, aryl, arylalkyl, or hydroxyalkyl.
6. The method of claim 3 wherein  $R_1$ - $R_{10}$  are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.
7. The method of claim 3 wherein said anthracene is selected from the group consisting of 1,2-dimethylantracene, 9,10-dimethyl anthracene, 7,8-dimethylantracene, 9,10-diphenylantracene, 9,10-dihydroxymethylantracene, 9-hydroxymethyl-10-methylantracene, dimethylantracene-1,2-diol, 9-hydroxymethyl-10-methylantracene-1,2-diol, 9-hydroxymethyl-10-methylantracene-3,4-diol, and 9, 10-di-m-tolylantracene.
8. The method of claim 3 wherein  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$  and  $R_{10}$  are hydrogen.
9. The method of claim 3 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are hydrogen.
10. The method of claim 3 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are hydrogen.
11. The method of claim 3 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_9$  and  $R_{10}$  are hydrogen.
12. The method of claim 3 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are hydrogen.
13. The method of claim 3 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$  and  $R_{10}$  are hydrogen.

14. The method of claim 1 wherein said ATPase inhibitor is nonhydrolyzable forms of ATP such as AMP-PNP.
15. The method of claim 1 wherein said a nuclease inhibitor is an analog of N-Ethylmaleimide, a heterodimeric adenine-chain-acridine compounds, or a quinilone such as Heliquinomycin.
16. The method of claim 1 wherein said polymerase inhibitor is an analog of aphidicolin, 1-(2'-Deoxy-2'-fluoro-beta-L-arabinofuranosyl)-5-methyluracil (L-FMAU) or 2',3'-dideoxyribonucleoside 5'-triphosphates.
17. The method of claim 1 wherein said antisense oligonucleotide comprises about 15 consecutive nucleotides that are complementary to the coding strand of a mismatch repair protein, wherein said antisense oligonucleotide specifically binds to said coding strand of said mismatch repair protein under physiological conditions and inhibits mismatch repair activity of said mismatch repair protein.
18. The method of claim 17 wherein said antisense oligonucleotide specifically binds to a regulatory portion on said coding strand of said mismatch repair protein.
19. The method of claim 17 wherein said antisense oligonucleotide is directed against the first six codons of a MMR gene message.
20. The method of claim 1 wherein said inhibitor of mismatch repair is introduced into a growth medium of a eukaryotic cell *in vitro*.
21. The method of claim 1 wherein said inhibitor of mismatch repair is introduced into a growth medium of a prokaryotic cell *in vitro*.

22. The method of claim 1 wherein said inhibitor of mismatch repair is introduced into a growth medium of a plant.
23. A method for generating a mutation in a gene of interest comprising exposing a cell comprising said gene of interest to a chemical mismatch repair inhibitor and testing said cell to determine whether said gene of interest comprises a mutation.
24. The method of claim 23 wherein said testing comprises analyzing a polynucleotide sequence of said gene of interest.
25. The method of claim 23 wherein said testing comprises analyzing a protein encoded by said gene of interest.
26. The method of claim 23 wherein said testing comprises analyzing the phenotype of said cell.
27. The method of claim 23 wherein said cell is a mammalian cell, and wherein said mammalian cell is made mismatch repair defective by exposing said mammalian cell to an inhibitor of mismatch repair.
28. The method of claim 27 further comprising removing the chemical inhibitor of mismatch repair after determining that said gene of interest comprises a mutation.
29. The method of claim 27 wherein said testing comprises analyzing a polynucleotide sequence of said gene of interest.
30. The method of claim 27 wherein said testing comprises analyzing a protein encoded by said gene of interest.
31. The method of claim 27 wherein said testing comprises analyzing the phenotype of

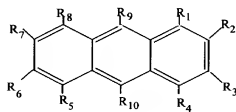
said cell.

32. A method for generating a mutation in a gene of interest comprising exposing an animal to a chemical inhibitor of mismatch repair and testing said animal to determine whether the gene of interest comprises a mutation.
33. The method of claim 32 wherein said animal is a mammal.
34. The method of claim 32 wherein said testing comprises analyzing a polynucleotide sequence of said gene of interest.
35. The method of claim 32 wherein said testing comprises analyzing a protein encoded by said gene of interest.
36. The method of claim 32 wherein said testing comprises analyzing the phenotype of said cell.
37. The method of claim 33 wherein said mammal is made mismatch repair defective by exposing said mammal to an inhibitor of mismatch repair.
38. The method of claim 37 further comprising removing said inhibitor of mismatch repair after determining that said gene of interest comprises a mutation.
39. A hypermutable transgenic mammal made by the method of claim 33.
40. A method for generating a mismatch repair defective plant comprising exposing said plant to an inhibitor of mismatch repair.
41. A method for generating a mutation in a gene of interest comprising growing a plant comprising said gene of interest, exposing said plant to an inhibitor of mismatch repair, and

testing said plant to determine whether said gene of interest comprises a mutation.

42. The method of claim 41 wherein said testing comprises analyzing a polynucleotide sequence of said gene of interest.
43. The method of claim 41 wherein said testing comprises analyzing a protein encoded by said gene of interest.
44. The method of claim 41 wherein said testing comprises analyzing the phenotype of said plant.
45. The method of claim 41 wherein said plant is made mismatch repair defective by exposing said plant to an inhibitor of mismatch repair.
46. A hypermutable plant made by the method of claim 40.
47. The plant of claim 46 wherein said plant is monocot.
48. The plant of claim 46 wherein said plant is dicot.
49. A method for screening for chemical inhibitors of mismatch repair comprising exposing an organism to a candidate compound and screening the DNA of said organism for microsatellite instability.
50. The method of claim 49 wherein said organism is a mammal.
51. The method of claim 49 wherein said organism is a microbe.
52. The method of claim 49 wherein said organism is a plant.

53. The method of claim 49 wherein said screening comprises monitoring endogenous microsatellites.
54. The method of claim 49 wherein said screening comprises the use of reporter expression genes, wherein said reporter expression genes comprise polynucleotide repeats within a coding region of said reporter gene.
55. The method of claim 54 wherein said reporter gene is  $\beta$ -glucuronidase.
56. A method for blocking mismatch repair activity *in vivo* comprising exposing a cell to an anthracene compound.
57. The method of claim 56 wherein said anthracene comprises the formula:



wherein R<sub>1</sub>-R<sub>10</sub> are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxy carbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO<sub>2</sub>, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and

wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl,

substituted aryl, and substituted heteroaryl are halogen, CN, NO<sub>2</sub>, lower alkyl, aryl, heteroaryl, aralkyl, aralkyloxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino;

and wherein said amino groups optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups.

58. The method of claim 57 wherein R<sub>5</sub> and R<sub>6</sub> are hydrogen.
59. The method of claim 57 wherein R<sub>1</sub>-R<sub>10</sub> are independently hydrogen, hydroxyl, alkyl, aryl, arylalkyl, or hydroxyalkyl.
60. The method of claim 57 wherein R<sub>1</sub>-R<sub>10</sub> are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.
61. The method of claim 57 wherein said anthracene is selected from the group consisting of 1,2-dimethylantracene, 9,10-dimethyl anthracene, 7,8-dimethylantracene, 9,10-diphenylantracene, 9,10-dihydroxymethylantracene, 9-hydroxymethyl-10-methylantracene, dimethylantracene-1,2-diol, 9-hydroxymethyl-10-methylantracene-1,2-diol, 9-hydroxymethyl-10-methylantracene-3,4-diol, and 9, 10-di-m-tolylantracene.
- R<sub>3</sub>, R<sub>4</sub>,
62. The method of claim 57 wherein R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are hydrogen.
63. The method of claim 57 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are hydrogen.
64. The method of claim 57 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are hydrogen.
65. The method of claim 57 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>9</sub> and R<sub>10</sub> are hydrogen.
66. The method of claim 57 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are hydrogen.



67. The method of claim 57 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$  and  $R_{10}$  are hydrogen.
68. The method of claim 23 further comprising exposing said cell to a mutagen.
69. The method of claim 32 further comprising exposing said animal to a mutagen.
70. The method of claim 68 or 69 wherein said mutagen is selected from the group consisting of N-methyl-N'-nitro-N-nitrosoguanidine, methane sulfonate, dimethyl sulfonate, O-6-methyl benzadine, ethyl methanesulfonate, methylnitrosourea, and ethylnitrosourea.
71. The method of claim 49 wherein the chemical is a MMR inhibitor wherein it induces microsatellite instability in MMR proficient cells but does not induce enhanced microsatellite instability in MMR deficient cells.